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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/465,491	12/16/99	CHANG S	RPA1002

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EXAMINER	
GOLDBERG, J	
ART UNIT	**PAPER NUMBER**
1655	3

DATE MAILED: 08/28/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/465,491	Applicant(s) CHANG ET AL.	
	Examiner Jeanine A Enewold	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-20 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-20 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Drawings

1. The drawings are approved by the draftsman.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 8-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of quantitating telomerase activity in a human sample based upon quantitating hTERT mRNA in a sample and determining the telomerase activity in a sample from the result obtained in step (a).

The specification teaches amplifying the hTERT mRNA in a sample with primers which encompass the beta-region from the full length hTERT mRNA sequence (pg. 26, lines 31-35). Samples were assayed for the Ct value and a standard curve was derived (pg. 31). Then the data was fit into a linear equation which predicts telomerase activity from the adjusted hTERT mRNA (pg. 36).

The art teaches the correlation of hTERT and telomerase activity is can not always be associated. Nakamura et al (Molecular Carcinogenesis, Vol. 25, pg. 312-

320, 1999) teaches that the hTERT expression level in both tumor and nontumor tissues does not always correlate with the telomerase activity level, suggesting posttranscriptional regulation of the expression of telomerase activity in gastrointestinal tissues (pg. 313, col. 1, para. 2). Nakamura teaches that "telomerase activity is controlled not only by transcription of hTERT but also at the posttranscriptional, translational, or posttranslational level (pg. 318, col. 1). Furthermore, Nakamura teaches several problems with the validity of telomerase assay including the presence of inhibitors of the Taq polymerase that caused under-estimation of telomerase activity or false-negative results (pg. 318, col. 2). Additionally, "isolated colonic crypts show a low level of telomerase activity measured by the TRAP assay but significant levels of hTERT expression measured by both RT-PCR and western blotting (pg. 319, col. 2). Additionally, Wu et al (Cancer, Vol. 86, No. 10, pg. 2038-2044, November 1999) teaches that a few samples were discordant for telomerase activity and hTERT expression. For example, 5 samples expressed hTERT mRNA but were negative for telomerase activity and six samples is not express hTERT mRNA but were positive for telomerase. Wu provides several reasons why this correlation failed in these cases (pg. 2041, col. 2). Furthermore, Aogi (Clinical Cancer Research, Vol. 5, pg. 2790-2797, October 1999) teaches that in some analyses of complex tissue samples, the correlation between hTERT mRNA and telomerase activity was not so apparent (pg. 2794, col. 2, para. 4). Aogi teaches that the use of hTERT for accurate analysis may be premature because of the incomplete understanding of the gene structure and the

patterns of hTERT mRNA splicing that may be important in the expression of the functional enzyme (pg. 2794, col. 2).

Thus, based upon the teachings in the specification and the art, the skilled artisan would be unable to practice the claimed invention as claimed. The art teaches several studies in which the hTERT mRNA level does not fully correlate to telomerase activity, as taught by Nakamura, Aogi and Wu. Thus, there is a great amount of unpredictability in determining the telomerase activity based upon the hTERT mRNA level. Those skilled in the art provide several problems which add to the unpredictability of predicting telomerase activity based upon the hTERT mRNA expression. The specification has determined a linear association which does not appear to take into account the asserted problems as found in the art. The instant application does not appear to overcome the limitations taught by Nakamura that telomerase activity is controlled not only by transcription of hTERT but also at the posttranscriptional, translational, or posttranslational level, the limitations taught by Aogi that some analyses of complex tissue samples, the correlation between hTERT mRNA and telomerase activity was not so apparent. The art provides reasonable unpredictability associating telomerase activity with hTERT expression.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-7, 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kilian et al (Human Molecular Genetics, Vol. 6, No. 12, pg. 2011-2019, 1997) or Ulaner et al (Cancer Research, Vol. 58, pg. 4168-4172, September 1998) in view of Hall et al (US 5,593,862, July 1997).

Kilian et al. (herein referred to as Kilian) teaches the beta deletion in the hTCS1 gene (also referred to as hTERT, see specification pg. 1). Kilian teaches that the beta-exon deletion encode truncated proteins. Kilian teaches regions surrounding the beta-exon deletion region (see Figure 5).

Ulaner et al. (herein referred to as Ulaner) teaches the beta-exon deletion (Figure 1). The 182-base pair deletion results in a nonsense mutation which truncates the protein before the conserves reverse transcriptase motifs (Figure 1). Ulaner teaches primer TERT-2620A which is the reverse primer in exon 9 which is used to amplify the beta-exon mutation. The beta deletion transcript did not code for an active reverse transcriptase (pg. 4170, col. 2). Ulaner teaches that in no instance has telomerase activity been expressed without full-length hTERT message (pg. 4171, col. 1).

Neither Kilian nor Ulaner specifically teach amplifying using a primer found in the beta-deletion.

However, Hall et al (US 5,593,862, July 1997) teaches the primers may be positioned within a deletion to detect the deletion. Specifically, Hall teaches "to further confirm the existence of the deletion, a series of primer from the deletion region were

designed" (col. 18, lines 55-60). "Primers which fall into the deletion region, even when paired with a primer outside the deletion, would not amplify" (col. 18, lines 58-62).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kilian or Ulaner to position the primers within the beta-exon deletion region, as taught by Hall. The ordinary artisan would have been motivated to have positioned the primers within the deletion, as taught by Hall, for the benefit of detecting the presence or absence of the beta-exon deletion. The ordinary artisan would have been further motivated to have detected the hTERT beta-exon mutation since Ulaner teaches that in no instance has telomerase activity been expressed without full-length hTERT message. Thus, detecting a beta-exon mutation within the hTERT gene would have the expected benefit of determining whether the telomerase activity is expressed. The art teaches primers which are external to the beta-exon deletion, however, it is known in the art, as taught by Hall that primers within the exon may also detect the absence of the mutation, thereby quantitating hTERT mRNA.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, *however*, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill

would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural homologues of the full length disclosed hTERT sequence concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. Thus, it would have been obvious for the skilled artisan to quantify hTERT by using primers which are either upstream of exon 7 or downstream of exon 8 and a second primer that is complementary to exon 8 since the beta-exon deletion was known in the art at the time the invention was made.

4. Claims 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kilian et al (Human Molecular Genetics, Vol. 6, No. 12, pg. 2011-2019, 1997) or Ulaner et al (Cancer Research, Vol. 58, pg. 4168-4172, September 1998) in view of Hall et al (US 5,593,862, July 1997) as applied to Claims 1-7, 14-16 above in further view of Stratagene Catalog (1988).

Neither Kilian, Ulaner, or Hall specifically teach placing the primers in a kit.

However, Stratagene teaches gene characterization kits.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods of Kilian, Ulaner and Hall to place the necessary reagents in kit, as taught by Stratagene, for the expected benefit of convenience and quality control. The ordinary artisan would be motivated to have packaged the primers necessary to amplify the beta-exon deletion

into a kit to reduce waste, save money, increase quality control and save time, as taught by Stratagene.

Conclusion

5. No claims allowable.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold
August 22, 2000

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP ~~1800~~ 1600